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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/759,519	CANTOR ET AL.	
	Examiner	Art Unit	
	Stephen Kapushoc	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☒ Claim(s) *1 and 9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending and examined on the merits.

This Office Action is in reply to Applicants' correspondence of 10/12/2006. No Claims are cancelled; no claims are withdrawn; claim 19 has been newly added; claims 1, 4, 6, 7, 9, 12, and 17 have been amended.

Applicants' remarks and amendments have been fully considered but are not found to be persuasive. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn.

This Action is made FINAL.

New Objections
Claim Objections

1. Claims 1 and 9 are objected to because of the following informalities:

Step (b) of claim 1 recites the phrase 'amplifying the diluted single molecule dilution and in a multiplex amplification reaction', where the word and is not needed in the phrase.

Step (d) of claim 1 recites the phrase 'from the genotypes of the at least the two polymorphic sites', where the phrase 'from the genotypes of the at least two polymorphic sites' (removing third 'the' from the phrase) is more correct.

Step (b) of claim 9 recites the phrase 'amplifying the diluted single molecule dilution and in a multiplex amplification reaction', where the word and is not needed in the phrase.

Includes New Grounds of Rejection
Claim Rejections - 35 USC § 112 2nd¶ - Indefiniteness

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-8 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8 and 19 are unclear over recitation of the phrase 'genotyping the at least two nucleic acid regions that contain at least one polymorphic site' in step (c) because step (b) of the claim requires the amplification of 'at least two nucleic acid regions comprising at least two polymorphic sites'. It is thus unclear if the claim requires that each 'region' comprises at least one polymorphic site, or if the 'at least two nucleic acid regions', when taken together, contain at least one polymorphic site. The claim may be made more clear if amended to recite, for example, 'at least two nucleic acid regions wherein each region comprises at least one polymorphic site' (in step (b)), and 'genotyping the at least two nucleic acid regions, wherein each region contains the least one polymorphic site' (in step (c)), if that is what applicant intends.

Claim 5 is unclear over the recitation of the phrase 'the polymorphism' because the base claim (claim 1) from which the rejected claim depends recites 'at least two polymorphic sites' (steps (b) and (d)) and 'at least one polymorphic site' (step (c)), thus it is unclear as to which of the multiple polymorphic markers is 'the polymorphism'.

Claim 6 is unclear over the recitation of the phrase 'contain a polymorphism that is a combination of one or more markers selected from' as it is unclear what is intended by, for example, a polymorphism that is a combination of a deletion and an insertion, or

a combination of an insertion and a substitution. It is unclear how a single polymorphism may be a combination of multiple different types of mutations. The claim may be made more clear if amended to recite 'contain a polymorphism that is selected from the group consisting of', if that is what applicant intends.

Response to Remarks

Applicants have asserted (Remarks page 9, ¶6) that in light of the amendments to the claims, the rejection of claim 5 as indefinite should be withdrawn. The examiner maintains that the recitation of 'the polymorphism' in claim 5 is unclear as claim 1 recites multiple polymorphisms (for example 'at least two polymorphic sties' and 'at least one polymorphic site'), thus it remains unclear to what polymorphic site claim 5 is referring to in the recitation of 'the polymorphism'.

The rejection is MAINTAINED.

New Grounds of Rejection
Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1, 5, 6, and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Furlong et al et al (1993).

Furlong et al teaches a method for the haplotype analysis of single sperm cells using multiplex PCR.

Regarding claim 1, Furlong et al teaches dilution of sperm from seminal fluid to a single cell (p.1192 – Flow-sorting of single sperm), where such a dilution is diluting any particular chromosome in the sperm cell to a single molecule dilution (relevant to step (a)). The reference further teaches a multiplex amplification (p.1192 – PCR of single sperm) with at least two different primer pairs, where each primer pair amplifies a region and each region has a polymorphic site, relevant to step (b). The reference further teaches the analysis of PCR products (Figure 1) which is the genotyping of the regions in the single nucleic acid molecule, relevant to step (c). Relevant to step (d), the reference teaches that the analysis of the genotyped polymorphic sites in the single sperm molecule allows for obtaiing the haplotype of the subject (Figure 1; p.1193 – Single-sperm analysis of three microsatellite markers).

Regarding claims 5 and 6, the reference teaches the analysis of microsatellite markers that are dinucleotide repeats (p.1191 – right col., lns.10-13), where the polymorphic forms may be considered for example, either a deletion or an insertion.

Regarding claim 19, the reference specifically teaches the use of 4 different primer pairs to amplify four microsatellite regions on chromosome 9 (p.1192 – PCR primers; PCR of single sperm).

New Grounds of Rejection
Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 4-6, 8, and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (as cited in the IDS) in view of Furlong et al (1993).

Ruano et al teaches a method for the analysis of haplotypes amplified from a single DNA molecule.

Ruano et al teaches that a nucleic acid sample is diluted to form a solution containing a single copy of the target molecule (p.6297 – Dilutions; Fig 3), relevant to step (a) of claim 1. Relevant to step (b), the reference further teaches the amplification of target DNA using a primer pair (GR5 and GR6) that amplify a region comprising polymorphic sites (Fig 1; p.6297 – Target for amplification) and subsequent analysis of the polymorphic positions (a TG deletion, two SNPs, and a TaqI RFLP site) in the amplified fragment (Fig 4). Relevant to step (c), Ruano et al teaches the genotyping of sites amplified from the single molecule dilution target DNA (Fig 4) by southern hybridization and restriction digestion, thus genotyping nucleic acid regions that contain polymorphisms. Relevant to step (d), the reference teaches that information regarding

the individual genotypes is combined to determine the haplotype of the subject (Fig 4; p.6298 – Typing and direct haplotype determination of SMP products).

Regarding claim 2, Ruano et al teaches that additional experiments are performed on sample DNA to resolve constituent haplotypes of heterozygous individuals (p.6298, right col., last paragraph; Fig. 3; Fig 4), and that each experiment followed the scheme present in Figure 3 of the reference, thus comprising steps (a)-(c) of claim 1. The reference specifically teaches that for 'Person B' the experiment was repeated five times, and that four haplotypes (each comprising the component genotypes) were resolved (Fig 4; p.6299 – Individual B).

Regarding claims 4-6, Ruano et al teaches the analysis of a haplotype comprising polymorphic sites that are single nucleotide polymorphisms and a dinucleotide insertion/deletion (Fig 1).

Ruano et al does not specifically teach an example in which a single molecule dilution is amplified in a multiplex PCR with multiple primer pairs, relevant to the limitation of claim 1 step (b). Ruano et al does not specifically teach the analysis of 12-18 genotype replicas, relevant to the limitations of claim 8.

Furlong et al teaches a method in which a single molecule dilution of a nucleic acid is amplified in a multiplex reaction for the determination of a haplotype (p.1192 – PCR of single sperm).

Regarding claim 19, the reference specifically teaches the use of 4 different primer pairs to amplify four microsatellite regions on chromosome 9 (p.1192 – PCR primers; PCR of single sperm).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the haplotype analysis methods of Ruano et al with the multiplex PCR methods of Furlong et al. One would have been motivated to do so because Furlong et al demonstrates the successful use of multiplex PCR for haplotype construction in the analysis of single molecules, and such a method would decrease the time and reagents required for the analysis of multiple polymorphic regions comprising a haplotype. One would have been further motivated to perform a multiplex PCR reaction based on the assertion of Ruano that distant segments of an intact template molecule can be analyzed by PCR with multiple primer pairs for direct haplotype determination (p.6300 – Discussion), which is a process that would be used in a multiplex reaction as taught by Furlong.

Regarding claim 8, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45). It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al to produce and analyze 12-18 replicas. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45).

Response to Remarks

Applicants argue (Remarks p.9-10) that Ruano et al do not teach the multiplexed amplification of a single molecule dilution of a target nucleic acid. This argument is moot in view of the new rejection of claims as set forth in the above rejection based on the teachings of Ruano et al in view of Furlong et al.

Applicants have traversed the rejection of the limitations of claim 8 as obvious in view of the teachings of Ruano et al. Applicants argue (Remarks p.11, ¶9), that the skilled artisan would have to balance accuracy with efficiency, and that Ruano et al teaches an example in which 5 replicates are analyzed achieves acceptable accuracy so that the skilled artisan would not be motivated to perform more than 5 replicates. This argument has been fully and carefully considered but is not found to be persuasive. While the particular example of Ruano asserts that in an example in which two out of six replicates remain unresolved the unresolved vials compromise efficiency but not accuracy (p.6300, left col., 2nd full ¶) the skilled artisan performing the method may wish to perform the assay with even greater accuracy than that of Ruano et al, and would recognize that with the analysis of multiple polymorphic positions (such as the four microsatellites as taught by Furlong et al) or with more restrictive dilutions, more replication would be performed to increase the accuracy.

Additionally, while Applicants argue that the instant specification teaches that 'replicas for the present analysis were typically performed about 12-18 times to increase efficiency', the example in the specification (p.20) in fact teaches that 'each 3-plex assay was repeated 12-18 times to evaluate the PCR and haplotyping efficiency'. Table 1 indicates that in 3 out of 12 attempts, replicates failed to genotype any of the three

SNPs. Thus it is not clear that in the example of the specification steps (a)-(c) were repeated 12-18 times (where step (c) requires genotyping a nucleic acid region) to form 12-18 genotypes.

The rejection of claim 8 as obvious in view of the teachings of Ruano et al is MAINTAINED.

8. Claims 3 and 9-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (as cited in the IDS) in view of Furlong et al (1993), and further in view of Drysdale et al (2000) (as cited in the IDS).

The teachings of Ruano et al in view of Furlong et al are applied to claims 3, and 9-11 as they were previously applied to claims 1, 2, 4-6, 8, and 19.

Regarding claim 11, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45).

Ruano et al in view of Furlong et al does not teach the comparison of a deduced haplotype with a haplotype from a control or a database of haplotypes to determine association of the haplotype with a biological trait, as required for claim 3, and step (e) of claim 9.

Drysdale et al teaches the use of β_2-adrenergic (β_2AR) receptor haplotypes in the prediction of response to albuterol (p.10486, left col., lns.6-8), which is a biological trait.

Regarding claim 3 and step (e) of claim 9 Drysdale et al teaches a collection of (β_2AR) haplotype pairs found in a cohort of asthmatics (p.10486, right col., lns.3-10; Table 2) (thus a database of haplotypes), as well as the association of the five most common haplotype pairs with patient response to albuterol (Fig.3; p.10487, left col., lns.1-25). The reference further teaches comparing a haplotype to the database of haplotypes and association data to determine association of the haplotype with a biological trait (Fig.3; p.10487, left col., lns.25-30).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have used the haplotype determination methods of Ruano et al in view of Furlong et al for the predictive analysis of haplotypes as taught by Drysdale et al. One would have been motivated to do so based on the assertion of Drysdale et al that haplotypes are more predictive of phenotype, and that individual SNPs may have poor predictive power as pharmacogenetic loci (p.10488, right col., lns.13-17). With specific regard to claim 11, it would be obvious to create and analyze numerous replicas, including producing 12-18 replicas, to increase the accuracy of the analysis. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45).

Response to Remarks

Applicants have traversed the previous rejection of claims with the argument that Ruano et al does not teach a multiplex PCR analysis of a single molecule as required

by the amended claims. This argument is moot in light of the new rejection of claims, necessitated by the amendments to the claims, as obvious in view of the teachings of Ruano et al in view of Furlong et al, and further in view of Drysdale et al.

New Rejection

9. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al (1990) (as cited in the IDS) in view of Furlong et al, and further in view of Ross et al (1998).

The teachings of Ruano et al in view of Furlong et al are applied to claim 7 as they were previously applied to claims 1, 2, 4-6, 8, and 19.

Ruano et al in view of Furlong et al does not teach the analysis of amplified polymorphic genotype markers using primer extension and mass spectrometric detection.

Ross et al teaches methods of multiplex genotyping using primer extension and mass spectrometry (p.1347, right col., lns.3-11). The reference teaches a method comprising the steps of simultaneous amplification of 12 polymorphic loci and subsequent multiplexed primer extension using oligonucleotide primers and ddNTPS (p.1350 – Experimental protocol, PCR). The reference further teaches analysis of the primer extension products by MALDI-TOF mass spectrometry (p.1350 – Experimental protocol, MS; Fig.2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the haplotype analysis methods of Ruano

et al in view of Furlong et al so as to incorporated the primer extension/mass spectrometry based genotype detection methods of Ross et al. One would have been motivated to use the methods of Ross et al based on the teachings of Ross et al that primer extension/mass spectrometry based methods eliminate excess handling and can resolve many possible genotypes/loci using a single non-fluorescent primer (p.1347, left col., ln.37).

10. Claims 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruano et al 1990 (as cited in the IDS) in view of Furlong et al (1993), and further in view of Rein et al (1998).

The teachings of Ruano et al in view of Furlong et al are applied to claims 12-18 as they were previously applied to claims 1, 2, 4-6, 8, and 19.

Ruano et al in view of Furlong et al teaches a method for the analysis of haplotypes amplified in a multiplex PCR reaction from a single DNA molecule. Ruano et al teaches the genotyping of sites amplified from the single molecule dilution target DNA by southern hybridization (Fig 4) and restriction digestion (Fig 3), and that information regarding the individual genotypes is combined to determine the haplotype of the subject (Fig 4; p.6298 – Typing and direct haplotype determination of SMP products). Thus, Ruano et al in view of Furlong et al teaches steps (b)-(e) of claim 12, and steps (b)-(d) of claim 17. With particular regard to step (c) of claim 17, Ruano et al teaches the amplification of samples diluted to a single molecule concentration, as well as amplification of more concentrated samples (Fig 3; p.6297 – Standard PCR).

Regarding claim 13, Ruano et al teaches that additional experiments are performed on sample DNA to resolve constituent haplotypes of heterozygous individuals (p.6298, right col., last paragraph; Fig. 3; Fig 4), and that each experiment followed the scheme present in Figure 3 of the reference, thus comprising steps (b)-(d) of claim 12. The reference specifically teaches that for 'Person B' the experiment was repeated five times, and that four haplotypes (each comprising the component genotypes) were resolved (Fig 4; p.6299 – Individual B).

Regarding claim 14, Ruano et al teaches repetition of experimentation to resolve genotypes (p.6298 – right col., last paragraph), and further teaches that errors in haplotype determination should be held in check by analyzing replicate vials (p.6300, left col., lns.43-45).

Regarding claim 18, Ruano et al teaches that additional experiments are performed on sample DNA to resolve constituent haplotypes of heterozygous individuals (p.6298, right col., last paragraph; Fig. 3; Fig 4), and that each experiment followed the scheme present in Figure 3 of the reference, thus comprising steps (b)-(d) of claim 17. The reference specifically teaches that for 'Person B' the experiment was repeated five times, and that four haplotypes (each comprising the component genotypes) were resolved (Fig 4; p.6299 – Individual B).

Ruano et al does not teach an analysis of a nucleic acid sample that contains epigenetically modified nucleotides by specifically treating modified nucleotides (relevant to step (a) of claim 12) or digestion of a nucleic acid sample with a methylation sensitive restriction enzyme (relevant to step (a) of claim 17).

Rein et al teaches method for the identification of 5-metyhlcytosine and related modifications in DNA genomes (Table 1; p.2255, right col., first full paragraph).

Regarding claim 12, Rein et al teaches methods for analysis of 5-methylcytosine (m^5C, which is a modified nucleotide) by treating genomic DNA with a composition that differentially affects epigentically modified nucleotides by converting non-methylated C to U, and not altering m^5C (p.2258 – Differential base modification by bisulfite), relevant to step (a) of claim 12, thus effectively creating polymorphisms (the content at a given nucleotide position can be a C if the position is methylated, or U (which behaves similar to a T in subsequent base pairing processes) if the position is nonmethylated) based on the epigenetic methylation modification (Fig 2).

Regarding claim 15, Rein et al teaches the analysis of 5-methylcytosine (m^5C), which is a methylated nucleotide (p.2258 – Differential base modification by bisulfite).

Regarding claim 16, Rein et al teaches the use of bisulfite for the treatment of a nucleic acid sample (p.2258 – Differential base modification by bisulfite; Table 1; p.2255, right col., ln.25).

Regarding claim 17, Rein et al teaches methods for analysis of methylated bases at specific DNA sites use modification-sensitive restriction endonucleases (Table 1; p.2257 - Modification-sensitive restriction endonucleases (MSREs); Fig 1). Relevant to step (a) of claim 17, the reference teaches the digestion of a sample with restriction enzymes that are sensitive to base modification (i.e. will not digest methylated sites) and restriction enzymes that require base modification (i.e. will only digest methylated sites) (p.2257, left col., lns.14-24; Fig 1). Relevant to step (e) of claim 17, Rein et al

teaches the analysis of the methylation dependent digestion of a sample by Southern analysis and PCR amplification (Fig 1; p.2258, left col., lns.15).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to have modified the haplotype determination methods of Ruano et al in view of Furlong et al so as to have included the methylation analysis methods of Rein et al. One would have bee motivated to do so because Rein et al teaches that m^5C in the genomes of eukaryotic cells plays a role in a variety of processes (p.2255, left col., first paragraph of introduction). One would have been motivated to use the bisulfite treatment of Rein et al (relevant to claims 12-16) because Rein et al teaches that such methods are highly sensitive, are amenable to rapid genomic sequencing, and provide positive display of m^5C (Table 1). One would have been motivated to use the MSRE method of Rein et al (relevant to claim 17 and 18) because Rein et al teaches that such methods provide a rapid analysis of large DNA regions, and are highly sensitive. With particular regard to step (e) of claim 17, the combination of the restriction enzyme digestion methods of Rein et al (as summarized in Fig 1 of Rein et al) and the haplotype determination methods of Ruano et al in view of Furlong et al would create a method where, for example, the DNA sample amplified by the multiplex PCR would be subjected to restriction digestion (as taught in Fig 1 of Rein et al) prior to amplification. Thus the determined haplotype would include polymorphic markers such as SNPs (determined by PCR as taught by Ruano et al) that are next to (e.g. the polymorphic sites would be adjacent to the cut site determined by the action of an m^5C-requiring restriction enzyme) the methylation site analyzed by the restriction enzyme.

With specific regard to claim 14, it would be obvious to create and analyze numerous replicas, including producing 12-18 replicas, to increase the accuracy of the analysis. One would have been motivated to create multiple genotype replicas based on the assertion of Ruano et al that such methods increase the accuracy of the analysis (p.6298 – right col., last paragraph; p.6300, left col., lns.43-45).

Response to Remarks

Applicants have traversed the previous rejection of claims with the argument that Ruano et al does not teach a multiplex PCR analysis of a single molecule as required by the amended claims. This argument is moot in light of the new rejection of claims, necessitated by the amendments to the claims, as obvious in view of the teachings of Ruano et al in view of Furlong et al, and further in view of Rein et al.

New Grounds of Rejection
Double Patenting

11. Claims 1-19 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-18 of copending Application No. 10/542,043 in view of Furlong et al (1993).

Claims 1-18 of the conflicting application are drawn to the same methods as claims 1-18 of the instant application. Claims 1-18 of the conflicting application do not recite the limitation that a multiplex amplification reaction is performed. However such multiplex amplification reactions were well known in the art at the time the invention was made.

Furlong et al teaches a method in which a single molecule dilution of a nucleic acid is amplified in a multiplex reaction for the determination of a haplotype (p.1192 –

PCR of single sperm). Regarding claim 19, the reference specifically teaches the use of 4 different primer pairs to amplify four microsatellite regions on chromosome 9 (p.1192 – PCR primers; PCR of single sperm).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods of the claims of the conflicting application to include a multiplex PCR reaction as taught by Furlong et al, and further to specifically include at least 4 different primer pairs as taught by Furlong et al. One would have been motivated to do so because Furlong et al demonstrates the successful use of multiplex PCR for haplotype construction in the analysis of single molecules, and such a method would decrease the time and reagents required for the analysis of multiple polymorphic regions comprising a haplotype.

This is a provisional obviousness-type double patenting rejection.

Conclusion

No claim is allowable. No claim is free of the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen Kapushoc
Art Unit 1634

Carla Myers

CARLA J. MYERS
PRIMARY EXAMINER